

A 7 year survey of acute hepatitis type B

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SUMMARY Epidemiological and clinical features of acute symptomatic hepatitis type B were evaluated in 51 otherwise healthy children and in 13 children receiving immunosuppressive treatment for leukaemia and malignancy, who were admitted to hospital with acute hepatitis B surface antigen (HBsAg) positive hepatitis during a period of 7 years. Blood transfusions, or intimate contacts with asymptomatic HBsAg carriers or with contaminated material during repeated admission to hospital were the possible sources of infection in the immunosuppressed patients, whereas percutaneous exposure was identified as the source in a minority of non-immunosuppressed patients. Features of the acute phase of the illness differed little between the two groups of patients (acute liver failure developed in one patient with leukaemia and in two untreated children). Conversely, chronic evolution was observed in 69% of immunosuppressed patients but in only 9% of untreated children and affected only patients born to HBsAg positive mothers (two of four patients) or patients presenting with papular acrodermatitis (both patients).

Acute symptomatic hepatitis type B in infants and children may present the whole clinical spectrum observed in adult patients¹; the disease may follow a benign course with final recovery; occasionally it may be fulminant either leading to death or eventually resolving.² In some cases it may develop into one of several chronic liver diseases of differing severity,³ including cirrhosis.⁴ Factors such as age at onset and administration of immunosuppressive treatment may influence the evolution of the disease. Few studies, however, have investigated the clinical course and outcome of acute hepatitis B in large series of consecutive paediatric patients.⁵ We report the results of a 7 year epidemiological and clinical study of acute hepatitis B in 51 consecutive, otherwise healthy children and in 13 children receiving immunosuppressive treatment for acute leukaemia or malignancy, who were admitted to hospital with symptoms of acute hepatitis B surface antigen (HBsAg) positive hepatitis.

Patients and methods

Between January 1975 and June 1981 155 children, aged three months to 12 years, with no underlying systemic diseases, were admitted to the Department of Infectious Diseases in Padua with acute viral hepatitis. This department serves a district of 600 000 inhabitants. Acute viral hepatitis was diagnosed on the basis of clinical history (which permitted exclusion of chronic liver disease or of

associated biliary diseases), recent onset of symptoms, signs of liver disease, and fivefold or higher increase in alanineaminotransferase activities above the upper normal value (<50 IU/l).

Samples of serum were obtained from each patient during the acute phase of the illness and in the follow up period and stored at -20°C until analysis. HBsAg was investigated by commercial radioimmunoassay (Abbott Laboratories). Selected serum samples were assayed for hepatitis B e antigen (HBeAg) and its antibody (anti-HBe) by commercially available radioimmunoassay kits (Abbott Laboratories).

Fifty one (32%) children (26 boys and 25 girls, mean age 6.3 (SD 3.5) years) had HBsAg positive serum during the acute phase of illness. During the same period of observation 13 children (five boys and 8 girls, mean age 7.9 (SD 3.9)) with leukaemia (10 patients) or malignancy (three) were referred from the oncology unit to our department with features of acute hepatitis B. All these patients were receiving, or had recently stopped receiving, immunosuppressive treatment.

In both immunosuppressed and non-immunosuppressed children the probable source of infection was assessed from the history recorded on admission. Repeat controls of liver function tests and of hepatitis B virus markers were performed during the children's stay in hospital and in the follow up period when children were seen every four months for at least one year in the outpatient clinic. Patients still

showing abnormal transaminase activities at 12 months were considered to have developed chronic hepatitis B. They subsequently underwent liver biopsy by the Menghini technique, with the informed consent of their parents, and were followed up further. Liver histological findings were interpreted according to De Groote *et al*⁶ and to Sheuer.⁷

Results

Epidemiological aspects. During the 7 years of our survey cases of hepatitis B formed a varying proportion of the annual overall number of hepatitis cases. The peak incidence (51%) occurred in 1975 and was related to an epidemic of acute hepatitis B caused by a contaminated gammaglobulin preparation. The incidence of hepatitis B was 29% in 1978 and 25% in 1981. A progressive reduction in the total number of cases of acute hepatitis was also observed during the period of survey with 37 cases seen in 1975, 26 in 1978, and 8 during the first 6 months of 1981. Table 1 shows the age distribution of both immunosuppressed and non-immunosuppressed children with acute hepatitis B and Table 2 summarises the possible sources of infection.

Of the 13 patients with leukaemia or malignancy, 11 had received transfusions with blood from volunteer donors screened for HBsAg by third generation techniques, and all 13 had been repeatedly admitted to hospital. Conversely, of the 51 non-immunosuppressed children, only three had been transfused with whole blood and five had received a commercially available preparation of gammaglobulins now known to have been contaminated with HBsAg.⁸ Six children had developed hepatitis during the first 6 months of life; two of them had received transfusions in the neonatal period, and four were born to HBsAg positive mothers. These four all became HBsAg positive during the third or fourth month of life; the mother of one developed acute hepatitis type B soon after delivery and was HBeAg positive at presentation, and the mothers of the other three were asymptomatic HBsAg carriers. (Two of them were anti-HBe positive at delivery, and the third was found to be HBeAg positive at the time when her child developed acute hepatitis.) Two non-immunosuppressed children had a family

Table 2 Possible sources of infection and risk factors in children with acute HBsAg positive hepatitis

	Immunosuppressed children (n=13)	Non-immunosuppressed children (%) (n=51)
Blood or blood derivatives	11	8 (15)
Recent admission to hospital	13	6 (12)
with surgery	2	6 (12)
Family outbreak of hepatitis	0	6 (12)
Mother hepatitis B surface antigen positive at delivery	0	4 (8)
Unknown	0	27 (53)

contact known to be a chronic HBsAg carrier, but serological testing of family members of our patients for HBsAg was not routinely performed.

Clinical features of the acute phase. All patients were either symptomatic (complaining of anorexia, fatigue, vomiting, and abdominal pain) or had jaundice (Table 3). Extrahepatic manifestations included arthralgia (two cases), urticarioid lesions (five cases), and maculopapular acrodermatitis (7 cases), which in two girls aged 3 and 4 years developed the typical features of papular acrodermatitis described by Gianotti,⁹ with adenomegaly and anicteric hepatitis.

No important clinical differences were observed between patients with or without underlying malignancy (Table 3). Three children with symptoms of less than two weeks' duration showed features of acute liver failure on admission, with acute jaundice and encephalopathy. The first patient was a 12 year old girl with leukaemia, who had received transfusions and in whom immunosuppressive treatment had recently been stopped; the second patient was a 3 month old boy born to an asymptomatic anti-HBe positive mother; and the third was a 5 month old girl who had received blood transfusions in the neonatal period.

Evolution of acute hepatitis B. The outcome of acute hepatitis was evaluated in 57 patients who could be followed up for at least one year after clinical onset (Table 4). Of the three patients with acute liver failure, one (the third) died within one week of admission; the other two recovered, with transaminase activities returning to normal 6 to 8 weeks after onset, after receiving symptomatic treatment and exchange transfusions. In the 43 patients who recovered, the clearance of HBsAg occurred at various intervals, ranging from one to 24 weeks, and preceded the return to normal of transaminase activities in 9 patients only.

Nine immunosuppressed patients with persistently increased transaminase activities remained HBsAg

Table 1 Age distribution of 64 children with acute HBsAg positive hepatitis

	Age (years)		
	0-1	1-5	5-12
No (%) immunosuppressed (n=13)	0	4 (31)	9 (69)
No (%) non-immunosuppressed (n=51)	6 (12)	19 (37)	26 (51)

Table 3 Clinical and biochemical features of acute hepatitis in the 64 children. (No important differences in the parameters examined were observed between immunosuppressed and non-immunosuppressed children)

	No (%) with			Mean (SD)	
	Symptoms	Extrahepatic manifestations	Jaundice	Alanineaminotransferase activity (normal < 50 IU/l)	Bilirubin concentration ($\mu\text{mol/l}$)
Immunosuppressed children (n = 13)	10 (77)	1 (8)	12 (92)	1710 (1098)	202 (139)
Non-immunosuppressed children (n = 51)	46 (90)	13 (25)	45 (88)	1148 (671)	139 (110)

Conversion: SI to traditional units—Bilirubin: 1 $\mu\text{mol/l}$ \approx 58.47 $\mu\text{g/100 ml}$.

positive at 12 months, at which time all of them were also found to be HBeAg positive in serum; liver biopsy specimens were taken in two cases, and both showed features of chronic active hepatitis. Two of the 9 patients subsequently died and three were lost to further follow up. All four patients that could be observed for up to two years remained HBsAg and HBeAg positive with fluctuating transaminase activities.

Of the four non-immunosuppressed children with evidence of continuing liver disease at 12 months, two were born to HBeAg positive mothers and the other two had presented with papular acrodermatitis. All four patients remained HBsAg and HBeAg positive and were asymptomatic throughout the observation period. Liver biopsy specimens taken during the second year of illness were consistent with chronic active hepatitis in three patients and with chronic lobular hepatitis in the fourth.

Discussion

Acute symptomatic hepatitis B in our region is rarely observed in children,¹⁰ unlike hepatitis A. The present data seem to indicate a trend toward a further reduction in the incidence of hepatitis B, coinciding with the reduction in the total number of cases of acute hepatitis in childhood, as also reported in other European countries.¹¹

Table 4 Evolution of acute hepatitis in 57 patients one year after onset

	Immunosuppressed children (n = 13)	Non-immunosuppressed children (n = 44)
Died of fulminant hepatitis	0	1 (2%)
Healed	4 (31%)	39 (89%)
Mean (SD) duration of:		
Abnormal alanine-aminotransferase activity (weeks)	4.0 (0.8)	5.4 (3.3)
Abnormal bilirubin concentration (weeks)	3.7 (0.9)	4.3 (1.6)
Increased alanine-aminotransferase activity after 12 months	9 (69%)	4 (9%)

In our patients, acute hepatitis B was seldom observed in children below one year of age and transmission of infection from mother to neonate occurred in only four children, who developed symptomatic illness within the fourth month of life. Indeed, acute hepatitis seems to be a rare clinical manifestation of infection transmitted in the neonatal period. Shiraki *et al.*¹² reported only three cases among 24 children who acquired infection from their HBsAg positive mothers and were born to anti-HBe positive or to HBeAg negative mothers. Our results not only confirm the possibility that children born to anti-HBe positive mothers may develop overt hepatitis but also indicate that the disease may be severe and, therefore, should be prevented.

In children with no underlying diseases, blood transfusions were found to play a minor epidemiological part and evidence of percutaneous exposure was also rare. In more than half of these patients, therefore, the source of infection remained undefined. Most of them, however, had probably acquired infection from contact with asymptomatic HBsAg carriers; infection with hepatitis B virus is endemic in Italy.

In the course of our survey a consistent number of children who developed HBsAg positive hepatitis had leukaemia or malignancy and were receiving immunosuppressive treatment. Routine testing for HBsAg had not been performed in these patients before the development of acute hepatitis, and we cannot, therefore, exclude the possibility that, in some cases at least, a reactivation of a latent infection may have occurred after withdrawal of immunosuppressive treatment.¹³ It is well known that children with cancer are at risk of acquiring viral hepatitis due to repeated blood transfusions while receiving immunosuppressive drugs. Indeed, 85% of this group of patients had received transfusions, although with blood from volunteer donors screened for HBsAg by third generation techniques. We cannot exclude, however, the possibility that contact with asymptomatic carriers or with contaminated material during repeated admissions to hospital may

have contributed to the spread of infection in this group of patients.

As regards the clinical aspects of the disease, extrahepatic manifestations were almost exclusively represented by cutaneous lesions; papular acrodermatitis, as described by Gianotti,⁹ affected young children; in older patients maculopapular lesions were associated with icteric hepatitis in the absence of adenomegaly. An unfavourable evolution of acute hepatitis was observed in 69% of immunosuppressed children in agreement with data reported by Malone *et al.*¹⁴ Among patients without underlying diseases, fulminant hepatitis developed in two, both below one year of age, and chronic evolution was observed in 9% of patients, all of whom were below one year of age or had papular acrodermatitis. The persistence of hepatitis B virus infection acquired in the neonatal period has been emphasised in several reports¹⁵⁻¹⁷ and has been attributed to a state of immunological tolerance due to immaturity of the immune system. In our study the persistence of hepatitis B virus infection was observed only in children born to HBeAg positive mothers; infants born to anti-HBe positive mothers developed an adequate response to hepatitis B virus. These data might suggest, according to the interpretation proposed by Shiraki *et al.*,¹² that viral charge may be the determinant in modulating the immune response to hepatitis B virus in neonates and infants. As regards acute hepatitis associated with papular acrodermatitis, Colombo *et al.* have reported chronic evolution of the illness in about one third of their patients.¹⁸ Such an unfavourable outcome has been related either to immaturity of the immune system, in younger patients, or to a genetic defect of the immune response.¹⁹ All four untreated children who developed chronic liver disease were persistently HBeAg positive in serum and three of them showed features of active hepatitis 12-24 months after the onset of illness. In spite of the severity of liver damage and of the persistence of active virus replication, the long term evolution of the disease in such patients remains unpredictable. In previous reports, we observed that HBeAg positive children with chronic active hepatitis (with or without a history of acute infection) may spontaneously seroconvert to anti-HBe, with subsequent return to normal of transaminase activities and disappearance of histological features of activity.^{20 21}

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